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(71) Applicant: **Bristol-Myers Squibb Company**
345 Park Avenue
New York, N.Y. 10154(US)

(72) Inventor: **Smith, David W.**
7 Silver Birch Lane
Clinton, Connecticut 06413(US)
Inventor: **Yocca, Frank D.**
38 Tibbals Bridge Road
Madison, Connecticut 06443(US)
Inventor: **Yevich, Joseph P.**
115 Crest Road
Southington, Connecticut 06489(US)
Inventor: **Mattson, Ronald J.**
65 Smithfield Avenue
Meriden, Connecticut 06450(US)

(74) Representative: **Kinzebach, Werner, Dr. et al**
Patentanwälte Reitstötter, Kinzebach und Partner Sternwartstrasse 4 Postfach 86 06 49
W-8000 München 86(DE)

(54) **Antimigraine alkoxypyrimidine derivatives.**

(57) Certain 1-indolylalkyl-4-[4-(5-alkoxy)-pyrimidinyl] piperazines and their pharmaceutically acceptable salts are useful in the treatment of vascular headache.

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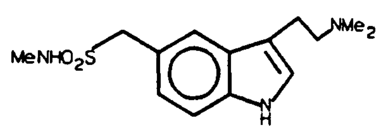
This invention generally pertains to heterocyclic carbon compounds having drug and bio-affecting properties and to their preparation and use. In particular the invention is concerned with 1,4-disubstituted piperazine derivatives wherein one substituent is indol-3-yl-alkyl and the other is an alkoxy-substituted pyrimidin-4-yl moiety. These compounds possess a unique serotonergic profile that renders them useful in treatment of vascular headaches of the migraine type.

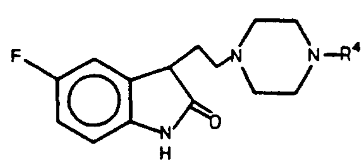
Archer disclosed a large series of CNS-depressant indolylalkylpiperazines in U.S. 3,188,313. Among a large number of possible substituents on the 4-nitrogen atom of the piperazine ring was pyrimidine (unsubstituted). In U.S. 3,562,278, Archer disclosed and claimed a series of 1-indolylethyl-4-substituted-piperazines. Among the possible 4-substituents listed is 2-pyrimidinyl, again unsubstituted. The pharmacologic action disclosed for these art compounds is general CNS and psychomotor depression which bear no relationship to an antimigraine effect. Thus the compounds of Archer do not suggest the alkoxypyrimidine antimigraine compounds of this invention.

Dowie, et al. disclosed a series of 3-alkylaminoindole derivatives as being potentially useful for the treatment of migraine in a published patent application, GB 2,124,210. One member of this series of compounds was specifically claimed in a later patent application of Oxford, GB 2,162,522, published February 5, 1986. This particular compound is known in the literature as sumatriptan.(1)



(1) Sumatriptan

A series of novel indoline derivatives were disclosed February 7, 1990 by Manoury, et al., in European patent application EPA 354,094. These compounds are described as being useful for treatment of various CNS disorders including depression, anxiety and migraine. Included among these art compounds are those of formula (2).



(2)

wherein R^4 is aryl, pyridine or quinoline moieties.

None of these art compounds make obvious the instant novel alkoxypyrimidine derivatives for treatment of migraine.

Migraine is a member of a broader class of headache which also comprises cluster headaches and other headaches believed to have a vascular implication in their etiology. These headaches are classified as vascular headaches. For a current summary of headache and its treatment see: Chapter 13: "Drugs Used to Treat Migraine and Other Headaches" in Drug Evaluations, 6th Edn., 1986, pages 239-253 American Medical Association, W.B. Saunders Co., Philadephia, PA.

Frequent irregularly-occurring episodes of headache afflict a large number of people but are usually acute in nature and of short duration. Relief of this type of headache is typically provided by mild analgesics such as aspirin or acetaminophen. Such headaches are quite common and, while painful and perhaps annoying, are seldom incapacitating and debilitating. Chronic recurrent headaches of the vascular category, however, usually lead to patient consultation with a physician due to pain severity which is often incapacitating.

Although there is no universally accepted classification system for headache, vascular headache, for the purposes of the present invention, refers mainly to migraine and cluster headaches. Migraine includes the common or classical type as well as migraine variants which would be familiar to one skilled in the art.

Other subtypes such as toxic vascular and hypertensive headaches, as well as some muscle-contraction and combined or mixed vascular-muscle headaches may also fall into a vascular-related headache category and be treatable by the present invention. It is appreciated by one skilled in the art that no single therapy is effective in all patients diagnosed with the same subtype of headache, thereby raising further uncertainties about headache classification.

Drugs most commonly used in treatment of headache fall into the following groups:
Ergot Alkaloids,
Beta-blocking Agents,
Calcium Channel Blocking Agents,
Antidepressants, and
Mixtures of these.

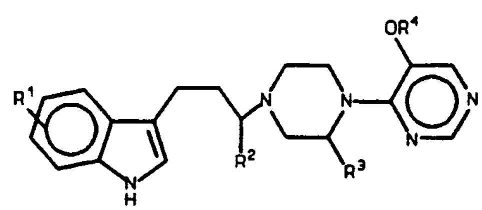
Management of recurring vascular headache is complicated by the lack of a single therapy which is effective in all patients with the same headache type and by the need to select either an abortive or prophylactic method of treatment for these headaches. Further complication involves the current use of drugs that cause dependence with extended use, such as ergotamine. Another important consideration for the present invention is that the more effective antimigraine agents in current use, e.g. the ergots, methysergide, produce severe use-limiting side-effects with long term usage.

Thus there is a need for a safe and effective drug for the treatment of migraine and related disorders which can be used either prophylactically or to alleviate an established headache.

The objectives of the present invention relate to the use of novel alkoxyprimidine derivatives to provide treatment of vascular headaches, particularly migraine; to processes for their preparation; to their pharmaceutical compositions and medical usage.

The method of the present invention is intended for the alleviation of vascular or vascular-related headache of which migraine and cluster are the best known specific examples. The method essentially involves administration of an alkoxypyrimidine derivative, or a pharmaceutically acceptable salt thereof, to a human in need of such treatment. For use in the instant method, oral and transnasal administration of pharmaceutical compositions containing the alkoxypyrimidine agent are preferred.

In a broad aspect, the present invention is concerned with alkoxypyrimidine derivatives having useful antimigraine serotonergic properties and characterized by compounds of Formula I.



I

In Formula I, R^1 is hydrogen, halogen or

$$CH_3SO_2\overset{\overset{\displaystyle R^5}{|}}{N}, -;$$

R^2, R^3 and R^5 are independently selected from hydrogen and lower alkyl; and R^4 is lower alkyl. The descriptive term "lower" is used herein to denote an organic radical containing from 1 to 4 carbon atoms.

Additionally compounds of Formula I also encompass all pharmaceutically acceptable acid addition salts and/or solvates thereof. The present invention is also considered to include stereoisomers as well as optical isomers e.g. mixtures of enantiomers as well as individual enantiomers and diasteromers, which arise as a consequence of structural asymmetry in certain compounds of the instant series. Separation of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art.

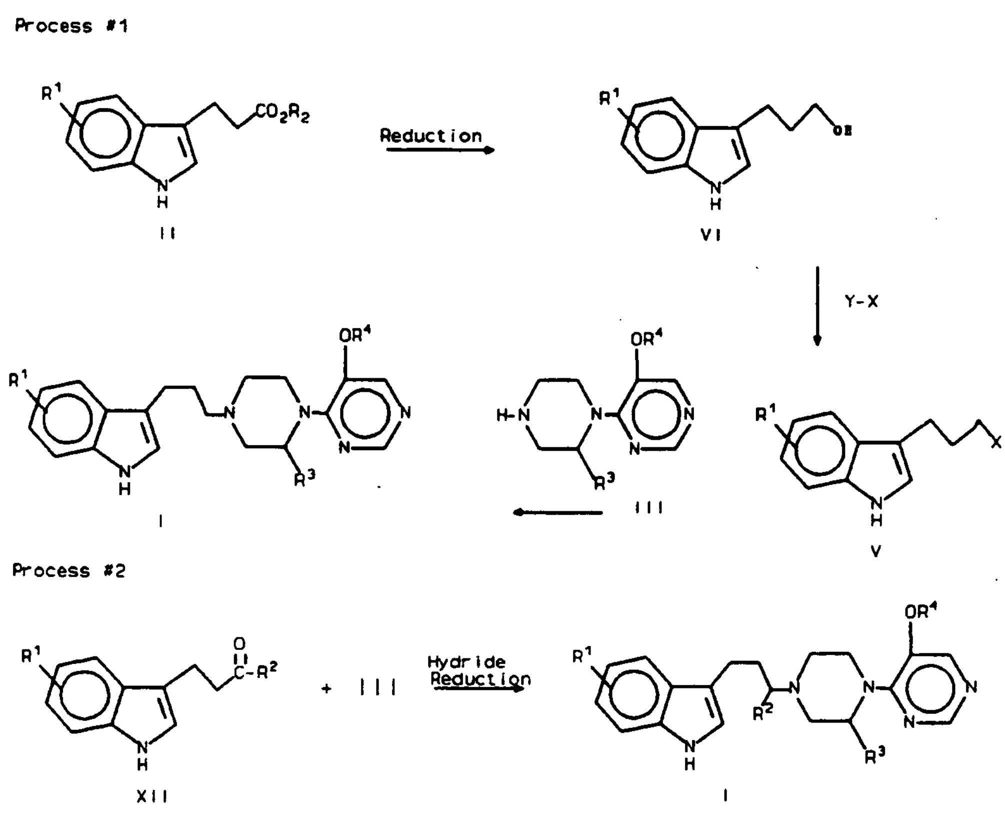
It is to be understood that, as used herein, halogen denotes fluorine, chlorine, bromine and iodine; with the term "lower alkyl" referring to both straight and branched chain carbon radicals of from 1 to 4 carbon

atoms inclusive. Illustrative of these radicals are carbon chains which can be methyl, ethyl, propyl, isopropy, 1-butyl, 1-methylpropyl 2-methylpropyl.

The pharmaceutically acceptable acid addition salts of the invention are those in which the counterion does not contribute significantly to the toxicity or pharmacological activity of the salt and, as such, they are the pharmacological equivalents of the bases of Formula I. They are generally preferred for medical usage. In some instances, they have physical properties which makes them more desirable for pharmaceutical formulation such as solubility, lack of hygroscopicity, compressibility with respect to tablet formation and compatibility with other ingredients with which the substance may be used for pharmaceutical purposes. The salts are routinely made by admixture of a Formula I base with the selected acid preferably by contact in solution employing an excess of commonly used inert solvents such as water, ether, benzene, methanol, ethanol, ethyl acetate and acetonitrile. The may also be made by metathesis or treatment with an ion exchange resin under conditions in which the anion of one salt of the substance of the Formula I is replaced by another anion under conditions which allow for separation of the desired species such as by precipitation from solution or extraction into a solvent, or elution from or retention on an ion exchange resin. Pharmaceutically acceptable acids for the purposes of salt formation of the substances of Formula I include sulfuric, phosphoric, hydrochloric, hydrobromic, hydroidic, citric, acetic, benzoic, cinnamic, mandelic, phosphoric, nitric, mucic, isethionic, palmitic, heptanoic, and others.

The compounds of Formula I can be prepared by means of the processes shown in Scheme 1.

SCHEME 1



For the two processes of Scheme 1, R^1 through R^4 are as defined hereinabove. The reagent Y-X represents an organic leaving group reagent wherein X is the leaving group fragment such as tosyl, mesyl, halide, sulfate, phosphate and so forth; and Y is either a proton or a counter ion: e.g. Y-X can be HBr or tosyl chloride and the like. "Hydride reduction" concerns intended reductive amination of XII by III, particularly the reduction of the initial complex of XII and III to provide product I. A preferred reagent for this

use in Process #2 is $NaCNBH_3$. The reagents of Scheme I and their acronyms are familiar to the practitioner skilled in organic synthesis and their structure and usage would be readily understood.

Process #1 in Scheme 1 comprises the reduction of an indole carboxylic acid or ester of formula II to the corresponding alcohol of formula VI which is converted to an activated intermediate of formula V in which the alcoholic moiety is now an organic leaving group. Reaction of intermediate V with a pyrimidinylpiperazine of formula III then provides product I.

Process #2 comprises combination of the indole intermediate of formula XII with a pyrimidinylpiperazine intermediate of formula III followed by treatment with sodium cyanoborohydride to give the product of formula I.

Reagents, solvents, and reaction conditions for the above described steps of the two processes would be known to one skilled in organic synthesis as all the steps comprise standard organic reactions, the details of which are readily available in the chemical literature. These processes may be adapted to variation in order to produce other compounds embraced by this invention but not specifically disclosed. Variations of the methods to produce the same compounds in somewhat different fashion will also be evident to one skilled in the art.

To provide greater descriptive detail, representative synthetic examples are provided hereinbelow in the "Description of Specific Embodiments" section.

Serotonin has been linked to the pathophysiology of migraine by accumulating evidence including increased excretion of serotonin metabolites following a migraine attack and a reduction in the serotonin content of blood platelets during the migraine headache. This latter effect appears to be specific for migraine and not a result of pain or stress. (Anthony, et al., "Plasma serotonin in migraine and stress", Arch. Neurol. 1967, 16: 544-552). More importantly, intramuscular injection of reserpine lowers plasma serotonin and induces a typical migraine-type headache in migraine sufferers. This induced headache can be alleviated by slow I.V. injection of serotonin creatinine sulfate. (Kimball, et al., "Effect of serotonin in migraine patients", Neurology N.Y., 1960, 10: 107-111).

Although serotonin has been shown to be effective in treating migraine attacks, its use in migraine is precluded by its side-effects such as restlessness, nausea, faintness, hyperpnea, facial flushing and parasthesias. (Lance, et al., "The control of cranial arteries by humoral mechanisms and its relation to the migraine syndrome", Headache, 1967, 7: 93-102). For this reason more specific serotonin agents, which would treat the migraine without all of the other actions, are potentially useful antimigraine medicaments. Accumulating findings have led to the perception that compounds with selectivity for the 5-HT_{1D} sub-type of serotonin receptors would be clinically efficacious in the treatment of migraine. In this regard the compounds of the instant invention demonstrate potent affinity and agonist activity at the 5-HT_{1D} site. The high potencies of these compounds is shown by IC_{50} values being below 5 nmolar.

Determination of 5-HT_{1D} binding properties was accomplished employing methodology such as that described by Heuring and Peroutka, J. Neurosci., 7(3), 1987, 894-903; with only minor modifications. In vitro IC_{50} (nM) test values were determined for the compounds of this invention employing tritiated serotonin.

Another aspect of the instant invention provides a method for treating a migraine sufferer which comprises systemic administration to the sufferer of a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

The administration and dosage regimen of compounds of Formula I is considered to be done in the same manner as for the reference compound sumatriptan, cf: Oxford, GB 2,162,522A. Although the dosage and dosage regimen must in each case be carefully adjusted, utilizing sound professional judgment and considering the age, weight and condition of the recipient, the route of administration and the nature and gravity of the illness, generally the daily dose will be from about 0.05 to about 10 mg/kg, preferably 0.1 to 2 mg/kg, when administered parenterally and from about 1 to about 50 mg/kg, preferably about 5 to 20 mg/kg, when administered orally. In some instances, a sufficient therapeutic effect can be obtained at lower doses while in others, larger doses will be required. Systemic administration refers to oral, intra-nasal, rectal and parenteral (i.e. intramuscular, intravenous and subcutaneous). Generally, it will be found that when a compound of the present invention is administered orally, a larger quantity of the active agent is required to produce the same effect as a smaller quantity given intra-nasally or parenterally. In accordance with good clinical practice, it is preferred to administer the instant compounds at a concentration level that will produce effective antimigraine effects without causing any harmful or untoward side effects.

The compounds of the present invention may be administered for antimigraine purposes either as individual therapeutic agents or as mixtures with other therapeutic agents. Therapeutically, they are generally given as pharmaceutical compositions comprised of an antimigraine amount of a compound of Formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, excipient or diluent thereof. Pharmaceutical compositions which provide from about 1 to 500 mg of the active

ingredient per unit dose are preferred and are conventionally prepared as tablets, lozenges, capsules, powders, aqueous or oily suspensions, syrups, elixirs, and aqueous solutions.

The nature of the pharmaceutical composition employed will, of course, depend on the desired route of administration. For example, oral compositions may be in the form of tablets or capsules and may contain conventional excipients such as binding agents (e.g. starch) and wetting agents (e.g. sodium lauryl sulfate). Solutions or suspensions of a Formula I compound with conventional pharmaceutical vehicles are employed for intra-nasal and parenteral compositions such as an aqueous solution for intravenous injection or an oily suspension for intramuscular injection.

The compounds which constitute this invention, their methods of preparation and their biologic actions will appear more fully from consideration of the following examples, which are given for the purpose of illustration only and are not be construed as limiting the invention in sphere or scope. In the following examples, used to illustrate the foregoing synthetic processes, temperatures are expressed in degrees Celsius and melting points are uncorrected. The nuclear magnetic resonances (NMR) spectral characteristics refer to chemical shifts (δ) expressed as parts per million (ppm) versus tetramethylsilane (TMS) as reference standard. The relative area reported for the various shifts in the ^1H NMR spectral data corresponds to the number of hydrogen atoms of a particular functional type in the molecule. The nature of the shifts as to multiplicity is reported as broad singlet (bs), singlet (s), multiplet (m), triplet (t) or doublet (d). Abbreviations employed are DMSO-d_6 (deuterodimethylsulfoxide), $CDCl_3$ (deuterochloroform) and are otherwise conventional. The infrared (IR) spectral descriptions include only absorption wave numbers (cm^{-1}) having functional group identification value. The IR determinations were employed using potassium bromide (KBr) as diluent. The elemental analyses are reported as percent by weight.

The following examples describe in detail the preparation of compounds of Formula I, as well as synthetic intermediates in each process. It will be apparent to those skilled in the art that modifications, both of materials and methods, will allow preparation of other compounds disclosed herein. From the foregoing description and the following examples it is believed that one skilled in the art is able to use the invention to the fullest extent.

A. Preparation of Intermediate Compounds

Some representative procedures for preparation of synthetic intermediate compounds utilized in the three processes of Scheme 1 are given hereinbelow. Most starting materials and certain intermediates (e.g. Formula II and V compounds), are either commercially available or procedures for their synthesis are readily available in the chemical literature allowing their full utilization by one skilled in the art of organic synthetic chemistry.

Compounds of Formula II

Example 1

General Method: 5-Fluoroindole-3-propionic acid

A modification of a procedure reported by Johnson [1] for the preparation of indole-3-propionic acid was used.

Thus, a solution of 5-fluoroindole (1.35 g, 0.010 mol) in 10 mL of acetic acid containing acrylic acid (1. 5 mL, 0.022 mol) and acetic anhydride (1.9 mL, 0.02 mol) was heated (oil bath) at 90°C under Ar for 5 days. The volatiles were then removed *in vacuo* and the residue was taken up in 3N NaOH. Insoluble material was removed by filtration and the filtrate was acidified with conc. HCl and then extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4) and evaporated to give the product (1.191 g, 57%) as a solid which was used without further purification: IR (neat) 3420, 1710 cm^{-1}; ^{1}Hnmr (200 MHz, $CDCl_3$) δ 7.94 (br s, 1H), 7.28-7.18 (m, 3H), 7.05 (d, J=2.5 Hz, 1H), 6.93 (dt, J=9.0, 2.6 Hz, 1H), 3.05 (t, J=7.5 Hz, 2H), 2.73 (t, J=7.6 Hz, 2H).

By appropriate modification of the general method, other Formula II compounds are readily obtainable.

Example 2

5-Chloroindole-3-propionic acid

[1]H.E. Johnson and D.G. Crosby, *J. Org. Chem*., *25*, 569 (1969)

The crude product was chromatographed (SiO_2/5-20% ethyl acetate-CH_2Cl_2) to give the title compound as a beige solid, m.p. 100-102°C: Yield = 41%; IR (neat) 3435, 1695 cm^{-1}; ^{1}Hnmr (200 MHz, $CDCl_3$) δ 8.00 (br s, 1H), 7.56 (d, J = 1.8 Hz, 1H), 7.27 (d, J = 8.7 Hz, 1H), 7.15 (dd, J = 8.6, 1.9 Hz, 1H), 7.05 (d, J = 2.3 Hz, 1H), 3.07 (t, J = 7.5 Hz, 2H), 2.75 (t, J = 7.4 Hz, 2H).

Example 3

6-Fluoroindole-3-propionic acid

The crude product was chromatographed (SiO_2/20% hexane-ethyl acetate) to give the title compound as a beige solid, m.p. 98-102°C: Yield = 23%, IR (neat) 3400, 1687 cm^{-1}; ^{1}Hnmr (200 MHz, $CDCl_3$) δ 7.97 (br s, 1H), 7.50 (dd, J = 8.7, 5.4 Hz, 1H), 7.07-6.99 (m, 2H), 6.89 (dt, J = 9.5, 2.2 Hz, 1H), 3.09 (t, J = 7.5 Hz, 2H), 2.76 (t, J = 7.4 Hz, 2H).

Compounds of Formula II

Example 4

3-[5-(Methylsulfonyl)aminoindolyl]propanoic acid

A. 5-(Methylsulfonyl)aminoindole

To a solution of 20 g of 5-aminoindole (151 mmol, 1.0 equiv.) and 31.5 mL (226 mmol, 1.5 equiv.) of triethylamine in 200 mL of CH_2Cl_2 at 0°C was added a solution of 12.8 mL (166 mmol, 1.1 equiv.) of methanesulfonyl chloride in 50 mL of CH_2Cl_2 dropwise. The solution was allowed to slowly warm to room temperature over 16 hours. The reaction mixture was concentrated and the residue dissolved in 800 mL of ethyl acetate. The organic layer was washed with 200 mL of water, 100 mL of 0.1 M HCl, 100 mL of saturated aqueous sodium bicarbonate and 100 mL of saturated aqueous sodium chloride. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to obtain 31.55 g (100%) of 5-methanesulfonamidoindole, m.p. 133-135°C.

B. 3-[5-Methylsulfonyl)aminoindolyl]propanoic acid

To a solution of 3.4 g (16.2 mmol, 1.0 equiv.) of 5-methanesulfonamidoindole in 15 mL of glacial acetic acid was added 2.2 mL (32.3 mmol, 2.0 equiv.) of acrylic acid and 3.1 mL (32.3 mmol, 2.0 equiv.) of acetic anhydride. The reaction mixture was heated at 90°C for 18 hours. The reaction mixture was cooled and volatile material was removed in vacuo. The residue was dissolved in 1 M sodium hydroxide with heating. Insoluble material was removed by filtration. The basic aqueous layer was acidified to pH 1 with concentrated aqueous hydrochloric acid. The aqueous layer was extracted with three 50 mL portions of ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated to give 5.0 g of a brown oil whose ^{1}HNMR and mass spectrum where consistent with formation of the carboxylic acid II. The material was used without further purification in subsequent reactions.

Compounds of Formula VI

Example 5

General Method: 5-Fluoro-3-(3-hydroxypropyl)indole

To a suspension of $LiA1H_4$ (433 mg, 11.4 mmol) in 20 mL of dry tetrahydrofuran at 5-10°C under Ar was added a solution of 5-fluoroindole-3-propionic acid (1.179 g, 5.7 mmol) in 5 mL of tetrahydrofuran. After 10 min the cooling bath was removed and the mixture was stirred at room temperature for 30 min and finally it was heated to reflux for 30 min. The resulting gummy mixture was allowed to cool to room temperature and then the reaction was quenched by the sequential addition of 0.5 mL of H_2O, 0.5 mL of 15% NaOH solution and finally 1.5 mL of H_2O. The mixture was then diluted with ethyl acetate, dried ($MgSO_4$) and evaporated to give a yellow-green oil. Flash chromatography (SiO_2/CH_2Cl_2-ethyl acetate = 2:1) afforded the product (918 mg, 83%) as an oil: IR (neat) 3420, 1583 cm^{-1}; ^{1}Hnmr (200 MHz, $CDCl_3$) δ 7.94 (br s, 1H), 7.28-7.20 (m, 2H), 7.03 (d, J = 2.4 Hz, 1H), 6.92 (dt, J = 9.1, 2.5 Hz, 1H), 3.71 (t, J = 6.4 Hz, 2H),

2.80 (t, J=7.5 Hz, 2H), 2.02-1.88 (m, 2H), 1.33 (br s, 1H).

Example 6

5-Chloro-3-(3-hydroxypropyl)indole

The title compound was prepared according to the general procedure to give a light brown oil which was used without further purification: Yield=96%; IR (neat) 3430, 3300, 1462 cm^{-1}.

Example 7

6-Fluoro-3-(3-hydroxypropyl)indole

The product was prepared according to the general procedure, except that the reaction was run at room temperature for 5 h. Standard work-up gave the title compound as a light brown gum: Yield=90%; IR (neat) 3420, 1630 cm^{-1}.

Example 8

3-[5-(Methylsulfonyl)aminoindolyl]propanol

To a solution of 2.02 g (7.16 mmol, 1.0 equiv.) of the crude indolepropionic acid (Example 4) in 10 mL of THF at 0°C was added 32.2 mL of a 1 M solution of borane-THF complex in THF dropwise. After the addition was complete, the ice bath was removed and the reaction mixture was allowed to warm to room temperature over thirty minutes. The reaction mixture was poured into saturated aqueous sodium bicarbonate and extracted with three 25 mL portions of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to yield 1.82 g of a yellow oil. This was chromatographed on silica gel using 5% methanol in methylene chloride containing 0.5% concentrated aqueous ammonia to yield 0.900 g (47% overall from 5-methanesulfonamidoindole)of VI.

Compounds of Formula V

Example 9

General Method: 5-Fluoro-3-(3-p-toluenesulfonyl oxypropyl)indole

To a solution of 5-fluoro-3-(3-hydroxypropyl)indole (917 mg, 4.75 mmol) in 20 mL of CH_2Cl_2 at 0°C under Ar was added triethylamine (728 µL, 5.23 mmol), followed by a solution of p-toluenesulfonyl chloride (994 mg, 5.23 mmol) in 5 mL of CH_2Cl_2 and then a catalytic amount of 4-dimethylaminopyridine (59 mg, 0.48 mmol). The reaction mixture was stirred at 0°C for 30 min and then at room temperature for 1 1/2 h. Evaporation of the mixture followed by chromatography (SiO_2/CH_2Cl_2) of the residue gave a gum. The gum was dissolved in ether and then the solution was diluted with hexane until an oil separated. Addition of a small amount of CH_2Cl_2 led to dissolution of the oil and crystallization of the product. Storage at - 20°C and then filtration and drying of the residue in vacuo gave the product (1.378 g, 84%) as fluffy white needles: m.p. 99°C; IR (CH_2Cl_2) 3470, 1360, 1178 cm^{-1}; ^{1}Hnmr (200 MHz, $CDCl_3$) δ 7.90 (br s, 1H), 7.61 (d, J=8.4 Hz, 2H), 7.30 (d, J=8.4 Hz, 2H), 7.27-7.20 (m, 1H), 7.08 (dd, J=9.6, 2.6 Hz, 1H), 6.96-6.94 (m, 1H), 6.88 (dd, J=9.0, 2.5 Hz, 1H), 4.06 (t, J=6.2 Hz, 2H), 2.74 (t, J=7.2 Hz, 2H), 2.42 (s, 3H), 1.99 (dq, J=7.2, 6.2 Hz, 2H).

Example 10

5-Chloro-3-(3-p-toluenesulfonyloxypropyl)indole

The crude product, produced via appropriate modification of Example 9, was chromatographed (SiO_2/ethyl acetate-hexane=1:1) to give the title compound as a solid, m.p. 80-83°C: Yield=80%; IR (neat) 3442, 1350, 1175 cm^{-1}.

Example 11

6-Fluoro-3-(3-p-toluenesulfonyloxypropyl)indole

The crude product, produced via appropriate modification of Example 9 was chromatographed (SiO_2/10-30% ethyl acetate-hexane) to give the title compound as an oil: Yield = 84%; IR (neat) 3410, 1353, 1178 cm^{-1}.

Example 12

3-(3-bromopropyl)-1H-indole

Phosphorus tribromide (17.4 g) in Et_2O (30 mL) was added dropwise to a Et_2O solution (100 mL) containing 3-(3-hydroxypropyl)indole (VI; 7.5 g) at 0° C with stirring and under N_2 atmosphere. After the addition was complete, the reaction was allowed to warm to 23° C and continuously stirred for 16 h. At the end of this time, the reaction was cooled to 0° C and ice (ca. 25 mL) added portionwise and stirred an additional 2 h. The organic phase was separated from the aqueous phase and the aqueous layer extracted with Et_2O. The combined organic phases were washed with sat. NaCl solution, dried with $MgSO_4$, filtered, and concentrated under reduced pressure to afford 3-(3-bromopropyl)indole (V; 1.51 g; 15%).

Example 13

3-[5-(Methylsulfonyl)aminoindolyl]propanol methanesulfonate

To a solution of 0.0920 g (0.343 mmol, 1.0 equiv.) of the indolepropanol in 3.5 mL of THF at 0° C was added 0.10 mL (0.686 mmol, 2.0 equiv.) of triethylamine followed by 0.04 mL of methanesulfonyl chloride. The reaction mixture was stirred at 0° C for thirty minutes then poured into 15 mL of saturated aqueous sodium bicarbonate. The aqueous layer was extracted with two five mL portions of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield 0.127 g of a yellow oil whose ^{1}HNMR indicated formation of the mesylate V.

Compounds of Formula III

Example 14

1-(5-Methoxy-4-pyrimidinyl)piperazine -- Method 1

To a solution of piperazine (38.40 g, 0.45 mole) in CH_3CN (225 mL) was added dropwise a CH_3CN (100 mL) solution containing 4-chloro-5-methoxypyrimidine (6.45 g, 0.04 mole) while under nitrogen atmosphere. After the addition was complete the reaction was heated at 60° C for 0.75 h. The reaction was concentrated under reduced pressure and the residue dissolved in CH_2Cl_2 and extracted with 5% $NaHCO_3$ and H_2O. The organic phase was dried with K_2CO_3, filtered, and concentrated under reduced pressure. Silica gel chromatography (CH_2Cl_2: MeOH:NH_4OH; 92:8:0.8) of the concentrate afforded II (7.63 g, 88.1%). Treatment of the base (1.0 g) with ethanolic HCl and crystallization from EtOH/i-PrOH yielded the hydrochloride salt of II (0.50 g, 39.1%, m.p. 207-211°).

1-(5-Methoxy-4-pyrimidinyl)piperazine -- Method 2

A. 4,6-Dihydroxy-5-methoxypyrimidine

A modified procedure of Bretschneider, Richter, and Klötzer, Monatsh. Chem. 96(6), 1661-76 (1965), was used. Absolute methanol (1.0 L) was added with ice bath cooling to sodium methoxide (175 g, 3.24 moles) in a 3 L round bottom flask. When the mixture had cooled to less than 20° C, dimethyl methoxymalonate (162.14 g, 1.00 mole) was added, and then solid formamidine acetate (104.11 g, 1.00 mole) was added. The mixture was stirred in the ice bath for 30 minutes, and then refluxed for 1 hour. The mixture was cooled in a cold water bath and then concentrated HCl (about 350 mL) was added until the mixture was strongly acidic on pH test paper. The precipitate was filtered, suspended in cold water (about 400 mL), and then filtered again. The white powder was dried *in vacuo* (125.84 g, 88.7%), and carried on

without further purification.

B. 4,6-Dichloro-5-methoxypyrimidine

A modified procedure of Bretschneider, Richter, and Klötze, Monatsh. Chem. 96(6), 1661-76 (1965), was used. A mixture of 4,6-dihydroxy-5-methoxy-pyrimidine (125.84 g, 0.887 mole), $POCl_3$ (700 mL), and N,N-diethylaniline (50 mL) was refluxed for 3 hours to give a brown solution. The solution was cooled and then the excess $POCl_3$ was removed in vacuo. Hexane (about 300 mL) was added to the residue and the mixture was refluxed with stirring. The hot hexane layer was decanted into a beaker, and residue treated two more times with hot hexane. The hexane extracts (total volume about 1 L) were concentrated in vacuo to give the crude product as a white solid (116.5 g, 73.3%). This material was recrystallized from pet ether to give colorless needles (92.0 g + 16.51 g second crop, 93.1% total recovery).

C. 6-Chloro-5-methoxy-4-(1-piperazinyl)pyrimidine

Piperazine (30 g) was dissolved in water (150 mL) and then solid 4,6-Dichloro-5-methoxypyrimidine (10.00 g, 55.8 mmole) was added. The mixture was vigorously stirred for 2 h at room temperature during which the 4,6-dichloro-5-methoxypyrimidine dissolved. The product was extracted from the aqueous reaction mixture with methylene chloride (yield 12.67 g, 99.2%). A sample (5 g) of the crude product was chromatographed on silica gel using a gradient of 20-40% methanol/ethyl acetate as the eluent. The product was then dissolved in acetonitrile and concentrated HCl added to give the salt as a white powder which was dried in vacuo to give the analytical sample (4.0 g, m.p.: 169-173° C bubbles).

Anal. Calcd for $C_9H_{13}N_4OC1$ • 1.5 HCl • 0.2 H_20				
	C, 37.67;	H, 5.24;	N, 19.53 H_2O;	1.26
Found:	C, 37.63;	H, 4.99;	N, 19.46 H_2O;	1.47

D. 1-(5-Methoxy-4-pyrimidinyl)piperazine

Piperazine (20 g) was dissolved in water (100 mL) in a Parr bottle and then solid 4,6-dichloro-5-methoxypyrimidine (5.00 g, 27.9 mmole) was added. The mixture was vigorously stirred for 2 h at room temperature during which the 4,6-dichloro-5-methoxypyrimidine dissolved. The stirring bar was removed, catalyst (10% Pd/C, 1.0 g) was added to the turbid solution, and the mixture was then hydrogenated (60 psi, 3 h) at room temperature. The catalyst was filtered off and the filtrate extracted 3 times with CH_2Cl_2. The CH_2Cl_2 extracts were dried over Na_2SO_4 and concentrated in vacuo to give a clear oil which solidified upon standing (3.34 g, 61.7%). This crude product was Kügelrohr distilled (yield 3.24 g), dissolved in acetonitrile, and concentrated HCl was added to precipitate the product as a white powder which was dried in vacuo - (4.32 g, 94.0% from crude product, m.p. 219-221.5° C).

Example 15

1-(5-Methoxy-4-pyrimidinyl)-2-methylpiperazine --Method 1

A. 1-(t-Butoxycarbonyl)-3-methylpiperazine

To a cold (-5° C) solution of 2-methylpiperazine (5.00 g, 0.05 mole) in 200 mL of CH_2Cl_2 under Ar was added a solution of di-t-butyl dicarbonate (10.9 g, 0.05 mole) in 100 mL of CH_2Cl_2 over 1 h. The resulting mixture was stirred at -5° C for 1 h and then at r.t. for 2 h. The solution was then washed (H_2O), dried (Na_2SO_4) and evaporated to give an oil which was chromatographed (SiO_2/ethyl acetate then ethyl acetate-MeOH-NH_4OH= 10:1:0.1) to give the product (4.30 g, 43%) as an oil. This material was used without further purification: ^1H nmr (200 MHz, $CDCl_3$) δ 4.15-3.75 (br s, 2H), 3.0-2.6 (m, 4H), 2.47-2.35 (m, 1H), 1.48 (s, 9H), 1.08 (d, J=6.7 Hz, 3H).

B. 1-(t-Butoxycarbonyl)-4-(5-methoxy-4-pyrimidyl)-3-methylpiperazine

A mixture of 1-(t-butoxycarbonyl)-3-methylpiperazine (2.0 g, 0.01 mole), 4-chloro-5-methoxypyrimidine

(1.5 g, 0.01 mole) and diisopropylethylamine (2.6 mL, 0.015 mole) in 25 mL of dry acetonitrile was heated to reflux under Ar for 60 h. The resulting solution was diluted with ether and then washed (H_2O, brine), dried (Na_2SO_4) and evaporated to give a gum. This gum was triturated with hexane (x3) and the supernatant was evaporated to give a gum. Flash chromatography (SiO_2/ethyl acetate-hexane = 1:1, then ethyl acetate) of this material gave first 4-chloro-5-methoxypyrimidine (0.4 g, 27%) and then the desired product (1.2 g, 30%) as a light pink solid: m.p. 70-72° C; IR (KBr) 1690, 1575 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.90 (s, 1H), 4.79 (br s, 1H), 4.4-3.8 (m, 3H), 3.86 (s, 3H), 3.35-2.90 (m, 3H), 1.48 (s, 9H), 1.21 (d, J = 6.7 Hz, 3H).

C. 1-(5-Methoxy-4-pyrimidinyl)-2-methylpiperazine

A solution of 1-(t-butoxycarbonyl)-4-(5-methoxy-4-pyrimidinyl)-3-methylpiperazine (1.70 g, 4.2 mmol) and trifluoroacetic acid (5 mL) in 50 mL of CH_2Cl_2 was stirred at r.t. under Ar for 18 h. The solution was evaporated, the residue was taken up in water and the mixture was basified (pH8) with 15% aqueous NaOH. The resulting (pH 8) mixture was extracted with ethyl acetate and the organic phase was washed (H_2O, brine), dried (Na_2SO_4) and evaporated to give a semi-solid. This material was taken up in ether, filtered to remove insoluble material and the solution was evaporated to give the product (0.80 g, 92%) as an oil. It was used without further purification: IR (neat) 3300, 1580, 1540 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.87 (s, 1H), 4.83-4.68 (m, 1H), 4.26-4.19 (m, 1H), 3.85 (s, 3H), 3.26-3.17 (m, 1H), 3.12-3.01 (m, 2H), 2.94-2.80 (m, 2H), 1.29 (d, J = 6.8 Hz, 3H).

4-(5-Methoxy-4-pyrimidinyl)-2-methylpiperazine --Method 2

A solution of 2-methylpiperazine (20 g) in water (100 mL) was reacted with solid 4,6-dichloro-5-methoxypyrimidine (5.00 g, 27.9 mmole) in a procedure similar to that given for Method 2 of Example 14. After hydrogenation and filtration of the catalyst, the product was extracted from the filtrate with CH_2Cl_2. The extracts were concentrated in vacuo, and the residue was Kügelrohr distilled to give a clear oil (5.46 g, 99.8%). The oil was dissolved in acetonitrile and concentrated HCl added to form the salt which was recrystallized from i-PrOH and dried in vacuo to give the product as a white powder (4.02 g, m.p. 185-188° C).

Example 16

1-(5-Ethoxy-4-pyrimidinyl)piperazine

A. 5-Ethoxypyrimidine

Sodium (2.89 g. 125.8 mmol) was dissolved in ethanol (110 mL) and 5-bromopyrimidine (10.0 g, 62.9 mmol) added. The reaction was heated at 120° in an autoclave for 17 h and then allowed to stand at 23° for 60 h. The ethanol was removed under reduced pressure and water (5 mL) added to the concentrate. The aqueous phase was extracted with CH_2Cl_2 (4 x 100 mL). The combined organic extracts were washed with saturated NaCl solution, dried with anhydrous K_2CO_3, filtered, and concentrated under reduced pressure. Silica gel chromatography (Hexane/EtOAc; 70:30) of the concentrate yielded 5-ethoxypyrimidine (2.00 g, 25.6%).

B. 5-Ethoxypyrimidine N-oxide

To a solution of 5-ethoxypyrimidine (2.00 g, 16.1 mmol) in CH_2Cl_2 (100 mL) was added 3-chloroperoxybenzoic acid, 50-60% tech. grade, (6.13 g, 17.7 mmol) and the reaction stirred at 23° C for 18 h. The reaction was extracted with water (2 mL) containing Na_2CO_3 (1.71 g, 16.1 mmol). The organic phase was dried with anhydrous K_2CO_3, filtered, and concentrated under reduced pressure to afford the N-oxide (1.75 g, 78%).

C. 4-Chloro-5-ethoxypyrimidine

To a solution of triethylamine (1.90 g, 18.6 mmol) and phosphorous oxychloride (2.87 g, 18.6 mmol) in $CHCl_3$ (60 mL) was added 5-ethoxypyrimidine N-oxide (1.75 g, 12.5 mmol) portionwise. After the addition was complete, the reaction was heated at reflux for 3 h. Upon cooling the mixture to 0° C, $CHCl_3$ (60 mL)

and water (10 mL) were added following by portionwise addition of $NaHCO_3$ (3.15 g, 37.5 mmol). After the effervescence had ceased, the organic phase was separated, dried with $MgSO_4$, filtered, and concentrated under reduced pressure to afford the chloro product (1.98 g) which was used without further purification.

D. 4-(Ethoxycarbonyl)-1-(5-ethoxy-4-pyrimidinyl) piperazine

A mixture of 4-chloro-5-ethoxypyrimidine (1.98 g, 12.5 mmol), ethyl 1-piperazinecarboxylate (5.93 g, 37.5 mmol) and micropulverized K_2CO_3 (5.18 g, 37.5 mmol) was heated at reflux in CH_3CN (75 mL) for 4 h. Upon cooling to 23°C, the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with water (5 mL). The organic phase was dried with anhydrous K_2CO_3,filtered, and concentrated under reduced pressure. Silica gel chromatography (CH_2Cl_2/MeOH;98:2) of the concentrate yielded product (2.29 g, 65%).

E. 1-(5-Ethoxy-4-pyrimidinyl)piperazine

To a KOH solution (10N, 20 mL) was added 4-(ethoxycarbonyl)-1-(5-ethoxy-4-pyrimidinyl)piperazine (2.29 g, 8.18 mmol). The reaction was heated at reflux for 24 h after which time the water was removed under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with saturated NaCl solution, dried with anhydrous K_2CO_3, filtered, and concentrated under reduced pressure. Silica gel chromatography (CH_2Cl_2/MeOH/NH_4OH;95:5:0.5) of the concentrate yielded III (0.71 g, 42%).

Products of Formula I

Example 17

1-[3-(5-Fluoro-1H-indol-3-yl)propyl]-4-(5-methoxy-4-pyrimidinyl)piperazine

To a solution of 5-fluoro-3-(3-p-toluenesulfonyloxypropyl)-indole (1.16 g, 3.34 mmol) in 50 mL of acetonitrile was added 1-(5-methoxy-4-pyrimidyl) piperazine (0.78 g, 4.0 mmol), KI (0.56 g, 4.0 mmol) and diisopropylethylamine (3.48 mL, 20.0 mmol) and the mixture was heated to reflux under Ar for 20 h. The resulting mixture was diluted with ethyl acetate, washed (H_2O, brine), dried (Na_2SO_4) and evaporated to give a gum. Flash chromatography (SiO_2/ethyl acetate-methanol 95:5) of this material gave a gum which was triturated with CH_2Cl_2-ether. Evaporation of the supernatant gave a foam which was recrystallized from ethyl acetate-hexane to give the product (0.70 g, 57%) as off-white crystals: m.p. 119-122°C; IR (KBr) 3190, 1580 cm^{-1}; ^{1}Hnmr (200 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.04 (br 2, 1H), 7.89 (s, 1H), 7.29-7.21 (m, 2H), 7.04 (d, J=2.2 Hz, 1H), 6.93 (dt, J=9.1, 2.4 Hz, 1H), 3.85 (s, 3H), 3.80 (t, J=5 Hz, 4H), 2.76 (t, J=7.5 Hz, 2H), 2.55 (t, J=5 Hz, 4H), 2.50-2.43 (m, 2H), 2.00-1.85 (m, 2H).

Anal. Calcd. for $C_{20}H_{24}FN_5O \cdot 0.5\ H_2O$:			
	C, 63.47;	H, 6.66;	N, 18.51.
Found:	C, 63.89;	H, 6.66;	N, 18.55.

Example 18

4-(5-Ethoxy-4-pyrimidinyl)-1-[3-(1H-indol-3-yl)propyl]piperazine hydrochloride hydrate

A mixture of 3-(1H-indole-3-yl)propyl 4-methylbenzenesulfonate (0.87 g, 2.65 mmol), 1-(5-ethoxy-4-pyrimidinyl)piperazine (1.10 g, 5.29 mmol), micropulverized K_2CO_3 (0.73 g, 5.29 mmol), and tetrabutylammonium hydrogen sulfate (0.04 g, 0.13 mmol) in CH_3CN (15 mL) was heated at reflux for 2.5 h under nitrogen atmosphere. The reaction was allowed to cool to 23°C and stand for 16 h. The reaction was concentrated under reduced pressure and the residue was dissolved in CH_2Cl_2 and extracted with water. The organic phase was dried with anhydrous K_2CO_3, filtered, and concentrated under reduced pressure. Silica gel chromatography (CH_2Cl_2/MeOH;98:2) of the residue afforded the free base (0.70 g, 72%) which was treated with ethanolic HCl to yield I (0.85 g, 99%; mp >230 °C) after crystallization from EtOH/MeOH.

Anal. Calcd. for $C_{21}H_{27}N_5O \cdot 2HCl \cdot 0.7H_2O$.				
	C 55.93,	H 6.80,	N 15.53,	H_2O 2.80
Found:	C 55.67,	H 6.66,	N 15.40,	H_2O 2.50

Example 19

1-[3-(1H-Indol-3-yl)propyl]-4-(5-methoxy-4-pyrimidinyl)piperazine hydrochloride

A mixture of 3-(1H-indol-3-yl)propyl 4-methylbenzenesulfonate (3.39 g, 10.31 mmol), 1-(5-methoxy-4-pyrimidinyl)-piperazine (2.0 g, 10.31 mmol), N,N-diisopropylethylamine (1.33 g, 10.31 mmol), and potassium iodide (0.26 g, 1.55 mmol) in dimethylformamide (6 mL) was heated at 50°C for 18 h under nitrogen atmosphere. The reaction was concentrated under reduced pressure. Silica gel chromatography (EtOAc:Et_3N:MeOH; 92:4:4) of the concentrate yielded the free base (2.35 g, 64.9%) which was treated with ethanolic HCl. Recrystallization from isopropanol afforded compound I (2.37 g, 57.5%; m.p. 221-224 C°).

Anal. Calcd. for: $C_{20}H_{25}N_5O \cdot 1.2\ HCl \cdot 0.25\ H_2O$				
	C, 60.10	C, 17.53	N, 6.74	H, 1.13 H_2O.
Found:	C, 60.18	C, 17.44	N, 6.72	H, 1.23 H_2O.

Example 20

1-[3-(1H-indol-3-yl)butyl]-4-(5-methoxy-4-pyrimidinyl)piperazine

To a mixture of 1-(5-methoxy-4-pyrimidyl)piperazine (1.55 g, 8.0 mmol), triethylamine hydrochloride (1.10 g, 8.0 mmol) and $NaCNBH_3$ (1.76 g, 28 mmol) in 20 mL of dry THF was added a solution of 3-(3-oxobutyl)indole [2], (0.75 g, 4.0 mmol) in 5 mL of THF and the mixture was stirred at room temperature under Ar for 20 h. The reaction mixture was then poured into 10% saturated $NaHCO_3$ and extracted with ethyl acetate (x2). The organic extract was washed with H_2O (x2) and then with 25 mL of 0.1N HCl. The resulting organic solution was extracted with 1N HCl (x2) and the aqueous phase was washed with CH_2Cl_2 - (x2) and then it was cooled at 0°C and basified with 50% aqueous NaOH. This gave a gummy precipitate which was extracted into ethyl acetate (x4) and the combined organic extract was then washed (brine), dried (Na_2SO_4) and evaporated to give a gum. Flash chromatography (SiO_2/acetonitrile-methanol; 95:5 then 80:20) of this material gave the pure product (968 mg, 66%) as a white foam.

The foam was taken up in CH_2Cl_2 and treated with excess ethanolic HCl. The solution was evaporated and the residue was again taken up in excess ethanolic HCl. Evaporation of the solution gave a light brown foam which was crystallized from hot methanol-acetone to give the hydrochloride (916 mg) as a white powder: m.p. 169-172°C (dec); IR (KBr) 3400, 1632, 1550, 1275 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ 11.68 (br s, 1H), 10.89 (s, 1H), 8.66 (s, 1H), 8.20 (s, 1H), 7.56 (d, J=7.4 Hz, 1H), 7.33 (d, J=7.7 Hz, 1H), 7.21 (d, J=2.3 Hz), 7.10-6.93 (m, 2H), 5.03-4.96 (m, 2H), 3.91 (s, 3H), 3.85-3.75 (m, 2H), 3.54-3.25 (m, 5H), 2.88-2.60 (m, 2H), 2.51-2.35 (m, 1H), 1.88-1.81 (m, 1H), 1.38 (d, J=6.5 Hz, 3H).

Anal. Calcd. for $C_{21}H_{27}N_5O \cdot 2HCl \cdot 1.4\ H_2O$:			
	C, 54.50;	H, 6.91;	N, 15.11.
Found:	C, 54.39;	H, 6.93;	N, 15.37.

Example 21

1-[3-(1H-indol-3-yl)propyl]-4-(5-methoxy-4-pyrimidinyl)-3-methyl-piperazine

[2] J. Szmuskovicz, etal., J. Am. Chem. Soc. 79, 2819 (1957).

A mixture of 3-(1H-indol-3-yl)propyl) 4-methylbenzenesulfonate (1.30 g, 4.0 mmol), 1-(5-methoxy-4-pyrimidinyl)-2-methylpiperazine (0.80 g, 3.9 mmol), freshly pulverized KI (0.66 g, 4.0 mmol) and diisopropylethylamine (3.5 mL, 20 mmol) in 25 mL of dry acetonitrile was heated to reflux under Ar for 18 h. The reaction mixture was then diluted with ethyl acetate, washed (H_2O, brine), dried (Na_2SO_4) and evaporated to give a gum. The gum was chromatographed (SiO_2/ethyl acetate, then 5% MeOH-ethyl acetate) to give the title compound (0.75 g, 54%) as a foam. The foam was taken up in excess methanolic HCl and the solution was evaporated and the residue was crystallized from methanol-isopropanol-ether to give 0.50 g of a solid. This was recrystallized from methanol-ether to give the hydrochloride (0.30 g) as an off-white solid: m.p. 185°C (dec); IR (KBr) 3400, 1630, 1544, 1500 cm^{-1}; ^1H nmr (200 MHz, d_6-DMSO) δ 11.00 (br s, 1H), 10.88 (s, 1H), 8.63 (s, 1H), 8.20 (s, 1H), 7.53 (d, J=7.6 Hz, 1H), 7.33 (d, J=7.7 Hz, 1H), 7.19 (d, J=2.1 Hz, 1H), 7.10-6.93 (m, 2H), 5.20 (br s, 1H), 4.90-4.82 (m, 1H), 3.90 (s, 3H), 3.70-3.48 (m, 3H), 3.11 (br s^9 4H), 2.76-2.69 (m, 2H), 2.16-2.13 (m, 2H), 1.51 (d, J=7.1 Hz, 3H).

Anal. Calcd. for $C_{21}H_{27}N_5O \cdot 2\ HCl \cdot 1.25\ H_2O$:			
	C, 54.72;	H, 6.89;	N, 15.20.
Found:	C, 54.67;	H, 7.08;	N, 15.17.

Example 22

1-[3-(5-Methanesulfonamido-1H-indol-3yl)propyl]-4-(5-methoxy-4-pyrimidinyl)piperazine

To a solution of 0.127 g (0.343 mmol, 1.0 equiv.) of mesylate (Example 13) in 3 mL of acetonitrile was added 0.12 mL (0.686 mmol, 2.0 equiv.) of N,N-diisopropylethylamine, 0.006 g (0.034 mmol, 0.1 equiv.) of potassium iodide and 0.133 g (0.686 mmol, 2.0 equiv.) of 1-(5-methoxy-4-pyrimidinyl)piperazine. The reaction mixture was heated to reflux for 16 hours. The reaction was cooled to room temperature and poured into saturated aqueous sodium bicarbonate. The aqueous layer was extracted with two five mL portions of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield 0.250 g of a yellow oil. This was chromatographed using 10% methanol in methylene chloride containing 1% concentrated aqueous ammonia to yield 0.0795 g (52%) of the base as an oil.

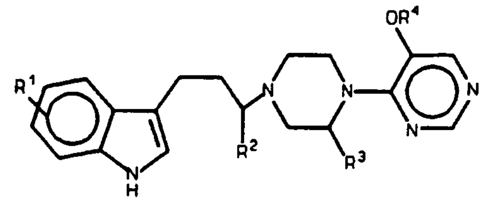
To a solution of 0.211 g (0.475 mmol, 1.0 equiv.) of the base in 5 mL of ethanol was added 0.95 mL (0.95 mmol, 2.0 equiv.) of 1 M HCl. The solution was concentrated to afford tan crystals. Recrystallization from hot ethanol yielded 0.1385 g of the hydrochloride ethanolate, $C_{21}H_{28}N_6O_3S \cdot 2.5HCl \cdot 1.4EtOH$, m.p. 150-152°C.

Anal. Calc.			
	C, 47.63;	H, 6.54;	N, 14.01.
Found:	C, 47.72;	H, 6.19;	N, 13.73.

By the appropriate modification of these experimental procedures, additional products of Formula I can be obtained by one skilled in organic chemical synthesis.

Table 1

Biological Activities of Some Formula I Compounds: Binding Affinity at the 5-HT_{1D} Site



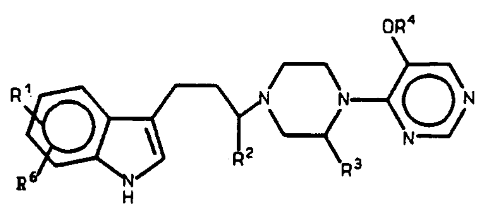
I

Ex. No.	R^1	R^2	R^3	R^4	5-HT_{1D} Binding IC_{50} (nM)
18	H	H	H	Et	2.0
19	H	H	H	Me	2.9
17	5-F	H	H	Me	3.0
23	5-Cl	H	H	Me	6.35
21	H	H	Me	Me	4.2
20	H	Me	H	Me	5.0
22	5-MSA*	H	H	Me	5.2

*MSA is methanesulfonamido-

Some additional compounds similar to those defined hereinbefore by Formula I also have antimigraine properties. For instance, these compounds also display selective binding and agonist properties at the 5-HT_{1D} sub-type of serotonin receptor. In general the entire series displays potent interaction at that receptor with nearly all compounds having IC_{50} values lower than 20 nmolar and the more potent members of the series having IC_{50} values less than 5 nmolar. The significance of these IC_{50} test values for 5-HT_{1D} binding sites, as it relates to antimigraine potential, has already been discussed for Formula I compounds.

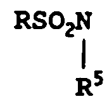
Formula XI (shown below) expands the scope of the invention to include these additional compounds which have the structure given here as Formula I'. The additional subject matter comprises compounds of Formula I'



I'

or a pharmaceutically acceptable acid addition salt and/or solvate thereof wherein

R^1 is lower alkoxy, phenyl-lower alkoxy, hydroxy, and



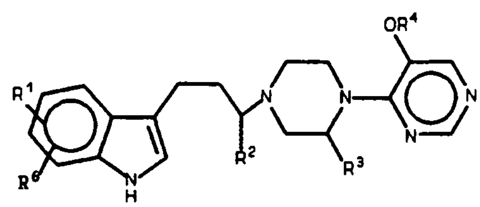
- in which R is lower alkyl and R^5 is hydrogen or lower alkyl;

R^2 and R^3 are independently selected from hydrogen and lower alkyl;

R^4 is lower alkyl; and

R^6 is hydrogen and halogen.

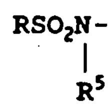
Thus the present redefined invention comprehends a compound of Formula XI



XI

or a pharmaceutically acceptable acid addition salt and/or solvate thereof wherein

R^1 is selected from hydrogen, halogen, lower alkoxy, phenyl-lower alkoxy, hydroxy, and



in which R is lower alkyl and R^5 is hydrogen and lower alkyl;

R^2 and R^3 are independently selected from hydrogen and lower alkyl;

R^4 is lower alkyl; and

R^6 is hydrogen and halogen.

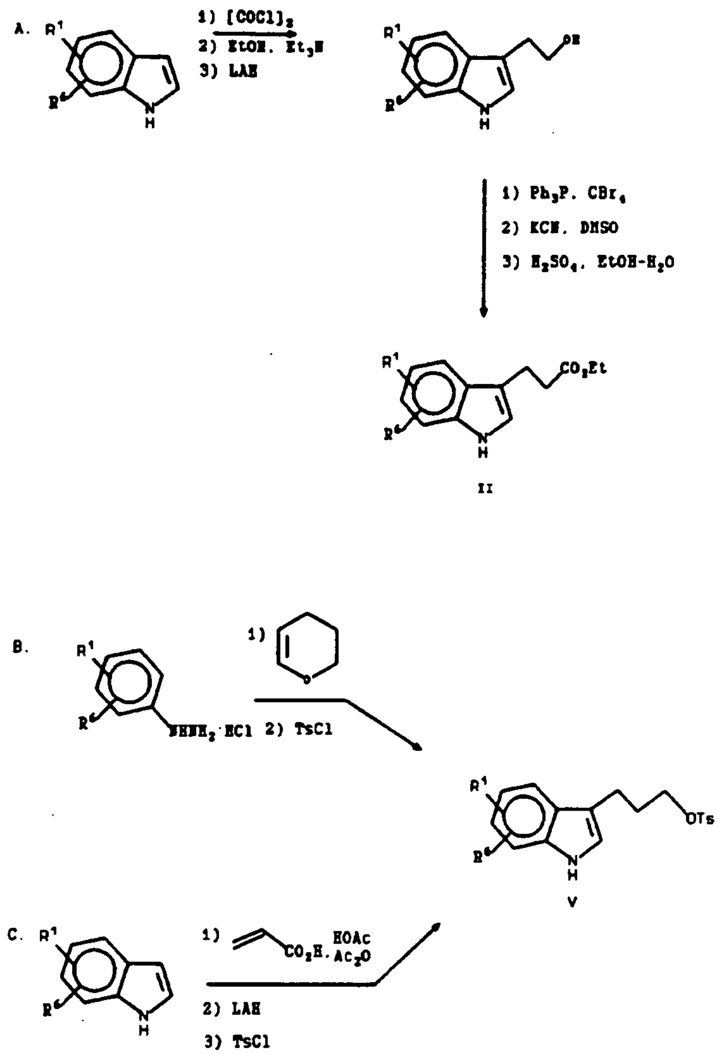
As can be seen, Formula XI encompasses both Formula I and Formula I' compounds. The preferred solvate form of compounds of Formula XI are hydrates, i.e. compounds complexed with water of hydration.

The compounds of Formula I' can be obtained by appropriate modification of synthetic procedures outlined in Scheme 1 and exemplified specifically as experimental examples hereinabove. In addition, synthetic procedures described hereinbelow are also useful for preparation of Formula I' and, with obvious modifications, Formula I compounds.

Scheme 2 depicts some additional synthetic schemes which represent variation of Process #1 of Scheme 1 which has been previously outlined and described. The intermediate compounds of Formula II or V are then carried on synthetically according to Scheme 1.

SCHEME 2. Additional synthetic Sequences for Intermediates II And V.

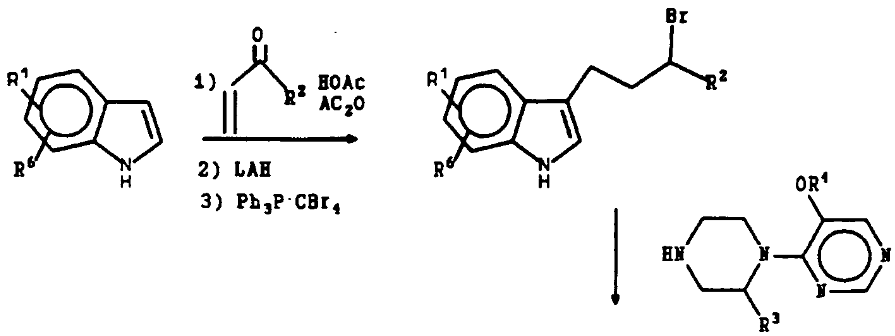
Sc



cf: Grandberg, et al. Izv Timiryazev. Sel'skokhoz. Akad., 1973, 4, 167-169. (CA 79:91889S).
Demerson, et al., J. Med. Chem., 1976, 19, 391.

Scheme 3 demonstrates a synthesis for Formula XI products wherein R^2 is lower alkyl.

SCHEME 3. XI Compounds with R^2 = lower alkyl (#H)

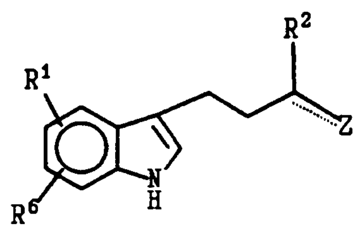


III

XI

In schemes 2 and 3, R^1-R^6 are as defined for compounds of Formula XI. The Grandberg, et al., and Demerson, et al. references describe indole preparations employing phenylhydrazines and dihydropyrans and dihydrofurans. In Scheme 3, a selected indole is alkylated with an R^2-vinylketone which is reduced to the corresponding alcohol and then converted to the bromo derivative by treatment with the triphenylphosphine-carbon tetrabromide complex. Reaction of this bromo intermediate with compound III gives a desired XI product having a lower alkyl R^2 group.

There is then the following unitary process for production of Formula XI compounds. This process comprises reacting a compound of Formula XV



XV

wherein R^1 is selected from hydrogen, halogen, lower alkoxy, phenyl-lower alkoxy, hydroxy, and

$$RSO_2\underset{\substack{| \\ R^5}}{N}-$$

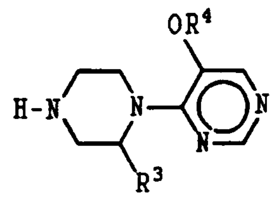
with R being lower alkyl and R^5 being hydrogen and lower alkyl;

R^2 is hydrogen and lower alkyl;

R^6 is hydrogen and halogen;

Z is selected from oxygen or an organic leaving group fragment such as tosyl, mesyl, halide, sulfate, phosphate, and

the dotted line is either a covalent bond, as when Z is oxygen and a double bond between carbon and oxygen is required, or no bond, as when Z is a leaving group fragment requiring only a single bond and a hydrogen atom is bonded to the terminal carbon atom; with a compound of Formula III:



III

wherein R^3 is hydrogen and lower alkyl; and
R^4 is lower alkyl
provided that if Z is oxygen, the reaction is carried out in the presence of a reducing agent.

Additional experimental procedures follow and they provide further guidance for the preparation compounds of the present invention.

Example 23

A. 5-(Methylsulfonyl)methylaminoindole

To a solution of 15.22 g (72.4 mmol, 1.0 equiv.) of 5-(methylsulfonyl)aminoindole in 400 mL of anhydrous THF at 0°C was added 32 mL (79.6 mmol, 1.1 equiv.) of a 2.5 M solution of n-BuLi in hexane dropwise. Stirring was continued for 30 minutes at 0°C followed by dropwise addition of 11.3 g (79.6 mmol, 1.1 equiv.) of methyl iodide. The reaction mixture was allowed to warm to room temperature and stir for 66 h. The mixture was poured into 1 L of ethyl acetate, washed with five 200 mL portions of 1 N NaOH and 200 mL of saturated aqueous sodium chloride. The organic layer was dried over anhydrous potassium carbonate, filtered and concentrated in vacuo to obtain 16.22 g (100%) of 5-(methylsulfonyl) methylaminoindole.

B. 1-[3-[5-(Methylsulfonyl)amino-1-H-indol-3-yl]propyl] -4-(5-methoxy-4-pyrimidinyl)-3-methylpiperazine.

To a solution of 1.68 g (4.85 mmol, 1.0 equiv.) of 3-[5-(methylsulfonyl)aminoindolyl]propanol methanesulfonate in 20 mL of acetonitrile was added 2.50 g (19.4 mmol, 4.0 equiv.) of N,N-diisopropylethylamine, 0.01 g (0.0485 mmol, 0.01 equiv.) of potassium iodide and 2.02 g (9.7 mmol, 2.0 equiv.) of 4-(5-methoxy-4-pyrimidinyl)-3-methylpiperazine. The reaction was heated to reflux for 48 h. The solution was cooled and poured into a mixture of 50 mL of ethyl acetate and 50 mL of saturated sodium bicarbonate. The organic layer was separated and the aqueous layer reextracted with three 25 mL portions of ethyl acetate. The combined organic layers were washed with 25 mL of saturated aqueous sodium chloride, dried over anhydrous potassium carbonate, filtered and concentrated in vacuo. The residue was chromatographed with 96:4 methylene chloride: methanol to yield 0.82 g (37%) of the desired material. The hydrochloride was prepared by addition of 2 equivalents of 9.68 M HCl in ethanol to the base in ethanol. The solution was concentrated and the hydrochloride recrystallized from ethanol. The salt was dried under high vacuum for four h at 65°C to yield 1-[3-[5-(methylsulfonyl)amino-1-H-indol-3yl]propyl]-4-(5-methoxy-4-pyrimidinyl)-3-methylpiperazine hydrochloride hydrate, m.p. 205-206°C.

Anal. Calcd. for $C_{22}H_{30}N_6O_3S \cdot 2HCl \cdot H_2O$:			
	C, 48.09;	H, 6.24;	N, 15.29
Found:	C, 47.98;	H, 5.98;	N, 15.18.

Example 24

1-[3-(5-Hydroxy-1H-indol-3-yl)propyl]-4-(5-methoxy-4-pyrimidinyl)piperazine

A mixture of 1-[3-(5-benzyloxy-1H-indol-3-yl)propyl]-4-(5-methoxy-4-pyrimidinyl)piperazine (Ex. 33; 1.40 g, 3.06 mmol) and 10% $Pd(OH)_2/C$ (0.85 g) in 25 mL of ethanol was hydrogenated at 30-40 psi in a Parr

shaker for 3.5 h. The mixture was filtered and then fresh catalyst (0.75 g) was added to the filtrate and hydrogenation was resumed at ca 45 psi for 22 h. The resulting mixture was filtered through Celite and the filtrate was evaporated to give a foam (0.995 g, 88%). The foam was taken up in methanolic HCl, whereupon a white solid precipitated. The solid was filtered, washed with cold methanol and then ether, and dried in vacuo to give the hydrochloride as a slightly pinkish solid (0.59 g), mp 215° C; IR (KBr) 3320 (Br) 1630, 1550 cm^{-1}; 7.07 (s, 1H), 6.80 (d, J = 2.1 Hz, 1H), 6.59 (dd, J = 2.2, 8.6 Hz, 1H), 4.91-4.84 (m, 2H), 3.90 (s, 3H), 3.8-3.4 (m, 7H), 3.2-3.0 (m, 4H), 2.69-2.62 (m, 2H), 2.2-2.0 (m, 2H).

Anal. Calcd. for $C_{20}H_{25}N_5O_2 \cdot 2.25$ HCl:			
	C, 53.44;	H, 6.11;	N, 15.58
Found:	C, 53.30;	H, 5.90;	N, 15.40

Example 25

3-[3-[4-(5-Methoxy-4-pyrimidinyl)-1-piperazinyl]pentyl] indole

A mixture of 3-(3-bromopentyl)indole (1.33 g, 5.0 mmol 1-(5-methoxy-4-pyrimidyl)piperazine (2.00 g, 10 mmol) finely pulverized K_2CO_3 (0.70 g, 5.1 mmol) and finely pulverized KI (0.90 g, 5.1 mmol) in 20 mL of acetonitrile was heated to reflux under Ar for 5 h. The cooled reaction mixture was diluted with EtOAc, washed (H_2O, brine), dried (Na_2SO_4) and evaporated to give a gum. Chromatography of this material (SiO_2/EtOAc then 10% MeOH-EtOAc) affords the product (0.65 g, 34%) as a gum. This gum was taken up in ether and then methanotic HCl was added. The resulting solid was filtered, washed with Et_2O and dried in vacuo to give an off-white solid (0.50 g), mp 145° C (dec); IR (KBr) 3400, 1633, 1550 cm^{-1};

Anal. Calcd. for $C_{22}H_{29}N_5O$.3HCl.0.75 H_2O:			
	C, 52.59;	H, 6.72;	N, 13.94
Found:	C, 52.70;	H, 6.34;	N, 13.91

By the appropriate modification of the foregoing schemes and experimental procedures, additional products of Formula XI can be obtained by one skilled in organic chemical synthesis.

Example 26

1-[3-[5-(Methylsulfonyl)methylamino-1-H-indol-3-yl] propyl]-4-(5-methoxy-4-pyrimidinyl)piperazine hydrochloride hydrate, m.p. 227-230° C was prepared in a similar manner starting from 5-(methylsulfonyl)-methylaminoindole.

Analys. calcd. for $C_{22}H_{30}N_6O_3S \cdot 2.2$ HCl $\cdot$ 1.0 H_2O:			
	C, 47.46;	H, 6.19;	N, 15.09
Found:	C, 47.32;	H, 5.82;	N, 14.87

Example 27

1-[3-[5-(Methylsulfonyl)methylamino-1-H-indol-3-yl] propyl]-4-(5-methoxy-4-pyrimidinyl)-3-methylpiperazine hydrochloride hydrate, m.p. 215-218° C was prepared in a similar manner starting from 5-(methylsulfonyl)-methylaminoindole.

Analys. calcd. for $C_{23}H_{32}N_6O_3S \cdot 1.3\ HCl \cdot 2.3\ H_2O$:			
	C, 49.20;	H, 6.80;	N, 14.97
Found:	C, 48.85;	H, 6.43;	N, 14.67.

Example 28

1-[3-[5-(Ethylsulfonyl)amino-1-H-indol-3-yl]propyl]-4-(5-methoxy-4-pyrimidinyl)piperazine hydrochloride hydrate, m.p. 140-145 °C was prepared in a similar manner starting from 5-(ethylsulfony)aminoindole.

Analys. calcd. for $C_{22}H_{30}N_6O_3S \cdot 2.3\ HCl \cdot 1.2\ H_2O$:			
	C, 46.85;	H, 6.20;	N, 14.90
Found:	C, 46.56;	H, 6.39;	N, 14.51.

Example 29

1-[3-[5-(Ethylsulfonyl)methylamino-1-H-indol-3-yl]propyl]-4-(5-methoxy-4-pyrimidinyl)piperazine hydrochloride hydrate, m.p. 223-225 °C was prepared in a similar manner starting from 5-(ethylsulfony)-methylaminoindole.

Analys. calcd. for $C_{23}H_{32}N_6O_3S \cdot 2.0\ HCl \cdot 0.1\ C_2H_6O$:			
	C, 50.49;	H, 6.36;	N, 15.23
Found:	C, 50.46;	H, 6.32;	N, 15.19.

Example 30

1-[3-[5-(Ethylsulfonyl)methylamino-1H-indol-3-yl]propyl]-4-(5-methoxy-4-pyrimidinyl)-3-methylpiperazine hydrochloride hydrate, m.p. 205-207 °C was prepared in a similar manner starting from 5-(ethylsulfonyl)-methylaminoindole.

Analys. calcd. for $C_{24}H_{34}N_6O_3S \cdot 0.9\ HCl \cdot 0.9\ H_2O \cdot 0.1\ C_3H_8O$:			
	C, 49.55;	H, 6.64;	N, 14.27
Found:	C, 49.22;	H, 6.66;	N, 14.01

Example 31

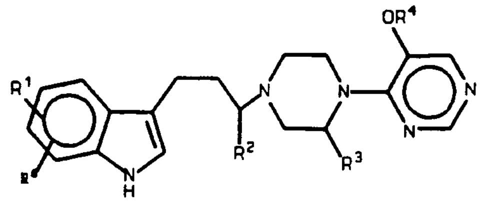
1-[3-[5-(Ethylsulfonyl)amino-1H-indol-3-yl]propyl]-4-(5-methoxy-4-pyrimidinyl)-3-methylpiperazine hydrochloride hydrate, m.p. 212-214 °C was prepared in a similar manner starting from 5-(ethylsulfonyl)aminoindole.

Analys. calcd. for $C_{23}H_{32}N_6O_3S \cdot 2.0\ HCl \cdot 0.4\ H_2O \cdot 0.3\ C_2H_6O$:			
	C, 50.04;	H, 6.52;	N, 14.84
Found:	C, 50.12;	H, 6.27;	N, 14.90

Additional Compound XI products and their 5-HT_{1D} binding activities are displayed in Tables 2 and 3.

Table 2

Additional Products of Formula XI



XI

Ex#	R^1	R^2	R^3	R^4	R^6	Mp(°C)
32	5-EtO-	H	H	Me	H	112-114°
33	5-PhCH$_2$O-	H	H	Me	H	180°(dec)*
34	5-MeO-	H	H	Me	H	130-150°(dec)*
35	5-F	H	H	Me	6-F	102-104°
36	4-F	H	H	Me	7-F	160-165°
37	5-F	H	H	Me	7-F	>250°(dec)*

* mp of HCl salt

Table 3

Binding Affinity at the 5-HT$_{1D}$ Site For Some Additional XI Products

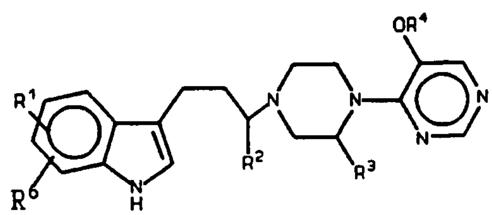
Example No.	5-HT$_{1D}$ Binding IC$_{50}$ (nM)
23	9.6
24	0.84
25	20.5
26	4.9
27	12.0
28	13.7
29	12.9
30	19.1
31	17.1
32	2.2
33	14.3
34	1.1
35	29.0
36	5.1
37	8.1

Table 3

Binding Affinity at the 5-HT_{1D} Site For Some Additional XI Products	
Example No.	5-HT_{1D} Binding IC_{50} (nM)
23	9.6
24	0.84
25	20.5
26	4.9
27	12.0
28	13.7
29	12.9
30	19.1
31	17.1
32	2.2
33	14.3
34	1.1
35	29.0
36	5.1
37	8.1

Claims

1. A compound of the following formula:



XI

wherein

R^1 is selected from hydrogen, halogen, lower alkoxy, phenyl-lower alkoxy, hydroxy, and

$$\begin{array}{l} RSO_2N- \; ; \\ \quad\quad\;\; | \\ \quad\quad\; R^5 \end{array}$$

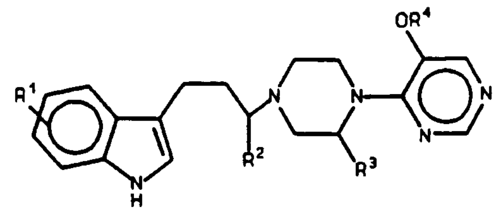
R^2, R^3 and R^5 are independently selected from hydrogen and lower alkyl; lower alkyl;

R^4 is lower alkyl;

R^6 is hydrogen and halogen.

or a pharmaceutically acceptable acid addition salt and/or solvate and/or stereoisomer thereof.

2. A compound of Formula I or a pharmaceutically acceptable acid addition salt thereof



I

wherein

R^1 is selected from hydrogen, halogen; or

R^2, R^3 and R^5 are independently selected from hydrogen and lower alkyl; and
R^4 is lower alkyl.

3. A compound according to claim 1 or 2 wherein R^1 is hydroxyl.

4. A compound according to claim 1 selected from 4-(5-ethoxy-4-pyrimidinyl)-1-[3-(1H-indol-3-yl)propyl]-piperazine; 1-[3-(1H-indol-3-yl)propyl]-4-(5-methoxy-4-pyrimidinyl)-piperazine; 1-[3-(5-fluoro-1H-indol-3-yl)propyl]-4-(5-methoxy-4-pyrimidinyl)-piperazine; 1-[3-(5-chloro-1H-indol-3-yl)propyl]-4-(5-methoxy-4-pyrimidinyl)-piperazine; 1-[3-(1H-indol-3-yl)propyl]-4-(5-methoxy-4-pyrimidinyl)-3-methylpiperazine; 1-[3-(1H-indol-3-yl)butyl]-4-(5-methoxy-4-pyrimidinyl)-piperazine; 1-[3-[5-(methylsulfonyl)-amino-1H-indol-3-yl]propyl]-4-(5-methoxy-4-pyrimidinyl) piperazine; 1-[3-[5-(methylsulfonyl)-amino-1H-indol-3-yl]propyl]-4-(5-methoxy-4-pyrimidinyl)-3-methylpiperazine; 1-[3-(5-hydroxy-1H-indol-3-yl)propyl]-4-(5-methoxy-4-pyrimidinyl)-piperazine; 3-[3-[4-(5-methoxy-4-pyrimidinyl)-1-piperazinyl]pentyl]indole; 1-[3-[5-methylsulfonyl)-methylamino-1H-indol-3-yl]propyl]-4-(5-methoxy-4-pyrimidinyl)piperazine; 1-[3-[5-methylsulfonyl)-methylamino-1H-indol-3-yl]propyl]-4-(5-methoxy-4-pyrimidinyl)-3-methylpiperazine; 1-[3-[5-ethylsulfonyl)amino-1H-indol-3-yl]propyl]-4-(5-methoxy-4-pyrimidinyl)piperazine; 1-[3-[5-ethylsulfonyl) methylamino-1H-indol-3-yl]propyl]-4-(5-methoxy-4-pyrimidinyl)piperazine; 1, 1-[3-[5-ethylsulfonyl)-methylamino-1H-indol-3-yl]propyl]-4-(5-methoxy-4-pyrimidinyl)-3-methylpiperazine; 1-[3-[5-ethylsulfonyl)amino-1H-indol-3-yl]propyl]-4-(5-methoxy-4-pyrimidinyl)-3-methylpiperazine; 1-[3-(5-ethoxy)-1H-indol-3-yl]propyl]-4-(5-methoxy-4-pyrimidinyl)piperazine; 1-[3-(5-benzyloxy-1H-indol-3-yl)propyl]-4-(5-methoxy-4-pyrimidinyl) piperazine; 1-[3-(5-methoxy-1H-indol-3-yl)propyl]-4-(5-methoxy-4-pyrimidinyl)-piperazine; 1-[3-(5,6-difluoro-1H-indol-3-yl)propyl]-4-(5-methoxy-4-pyrimidinyl)piperazine; 1-[3-(4,7-difluoro-1H-indol-3-yl)propyl]-4-(5-methoxy-4-pyrimidinyl)piperazine; 1-[3-(5,7-difluoro-1H-indol-3-yl)-propyl]-4-(5-methoxy-4-pyrimidinyl)piperazine, or a pharmaceutically acceptable acid addition salt thereof, and/or solvate and/or stereoisomer thereof.

5. 1-[3-(5-fluoro-1H-indol-3-yl)propyl]-4-(5-methoxy-4-pyrimidinyl)piperazine or a pharmaceutically acceptable acid addition salt and/or solvate thereof.

6. A pharmaceutical formulation which comprises as an active ingredient a compound, as claimed in any one of claims 1-5, associated with one or more pharmaceutically acceptable carriers, excipients or diluents therefore.

7. A pharmaceutical formulation according to claim 6 wherein the formulation is in unit dosage form.

8. A pharmaceutically formulation which comprises as an active ingredient 1-[3-(5-fluoro-1H-indol-3-yl)-propyl]-4-(5-methoxy-4-pyrimidinyl)piperazine associated with one or more pharmaceutically acceptable carriers, excipients or diluents thereof.

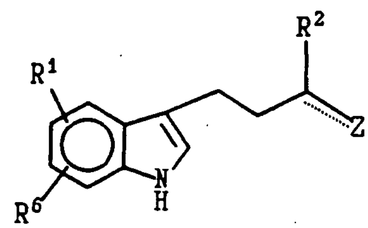
9. A pharmaceutical formulation according to claim 8 wherein the formulation is in unit dosage form.

10. A compound as claimed in any of one of claims 1-5 for use as an antimigraine agent.

11. 1-[3-(5-fluoro-1H-indol-3-yl)propyl]-4-(5-methoxy-4-pyrimidinyl)piperazine for use as an antimigraine agent.

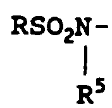
12. A pharmaceutical formulation as claimed in any of claims 6-9 for use as an antimigraine formulation.

13. A process for preparing a compound as claimed in any one of claims 1-5 which comprises reacting a compound of Formula XV



XV

wherein R^1 is selected from hydrogen, halogen, lower alkoxy, phenyl-lower alkoxy, hydroxy, and



with

R being lower alkyl and R^5 being hydrogen and lower alkyl;

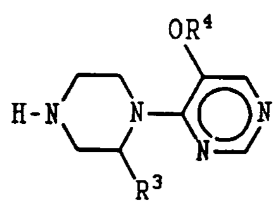
R^2 is hydrogen and lower alkyl;

R^6 is hydrogen and halogen;

Z is selected from oxygen or a leaving group fragment selected from tosyl, mesyl, halide, sulfate and phosphate; and

the dotted line is either a covalent bond as when Z is oxygen or no bond as when Z is a leaving group fragment and the carbon atom is then bonded to another hydrogen;

with a compound of formula III



III

wherein R^3 is hydrogen and lower alkyl; and

R^4 is lower alkyl

provided that if Z is oxygen, the reaction is carried out in the presence of a reducing agent.

European
Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 91 11 0376

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 345 808 (BRISTOL-MYERS COMPANY) * pages 1 - 9, line 30 * - - -	1,6	C 07 D 403/12 C 07 D 403/14 A 61 K 31/40 A 61 K 31/505
A	EP-A-0 242 939 (GLAXO GROUP LIMITED) * pages 1 - 2, line 32 * - - -	1,6	
A	DE-B-2 110 534 (SUMITOMO CHEMICAL CO.,LTD.) * the whole document * - - -	1,6	
A,D	US-A-3 562 278 (SYDNEY ARCHER) * column 1 - line 56 * * column 4, lines 20 - 55 * - - -	1,6	
A	CHEMICAL ABSTRACTS, vol. 93, no. 23, 08 December 1980 Columbus, Ohio, USA Trubitsyna,T.K. et al.: "Pharmacological properties of some indolylalkyl derivatives of & Farmakol.Toksikol.[Moscow] 1980, vol.43,no.5,pages 530-6.[Russ]. page 18; column 1; ref. no. 215274Y * abstract * - - - - -	1,6	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C 07 D 403/00 C 07 D 209/00

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
Berlin	07 October 91	KYRIAKAKOU G

CATEGORY OF CITED DOCUMENTS

X: particularly relevant if taken alone
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